

Resting heart rate in patients with stable coronary artery disease and diabetes: a report from the Euro Heart Survey on Diabetes and the Heart

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Aims

Epidemiological studies suggest that resting heart rate (RHR) is an independent predictor of cardiovascular and all-cause mortality. Still, this parameter has never been specifically assessed in patients with diabetes mellitus (DM). This study describes the association between RHR and cardiovascular events (CVE) in patients with coronary artery disease (CAD) with and without DM.

Methods and results

The Euro Heart Survey on Diabetes and the Heart enrolled 2608 patients with stable CAD, of these 780 (30%) had known DM. Resting heart rate was registered in 2507 (96%) patients: 1756 (96%) without and 751 (96%) with DM. Patients were followed with respect to CVE (all-cause mortality, non-fatal myocardial infarction, and stroke) for 1 year. Overall, median RHR was 70 (62–78) b.p.m. The RHR quartile stratification was significantly associated with outcome in the overall population ($P = 0.002$ and $P = 0.021$ for survival and CVE, respectively), whereas it was not in patients without DM. In patients with DM, the RHR quartiles correlated with survival ($P = 0.032$). In an adjusted regression model performed in patients without DM, RHR associated with neither survival [hazard ratio (HR): 0.97, 95% confidence interval (CI): 0.74–1.27; $P = 0.804$] nor CVE (HR: 0.85, 95% CI: 0.71–1.01, $P = 0.068$). In contrast, a 10-b.p.m. increase in RHR was independently associated with survival (HR: 1.34, 95% CI: 1.06–1.69, $P = 0.015$), but not with CVE (HR: 0.99, 95% CI: 0.84–1.18; $P = 0.359$) in patients with DM.

Conclusion

The present report, based on patients with stable CAD, is the first to reveal that the association between RHR and CVE seems to subsist in those with DM, however, not in those without DM.

Keywords

Resting heart rate • Coronary artery disease • Diabetes mellitus • Prognosis

Introduction

Over the last 25 years, a significant association between resting heart rate (RHR) and all-cause and cardiovascular mortality has been reported in the general population and in patients with various cardiovascular diseases including hypertension, acute myocardial infarction (AMI), and heart failure or left ventricular dysfunction.^{1–5} On the basis of this evidence, RHR has been included in risk assessment indices for the general population⁶ and for patients following acute coronary syndromes⁷ and AMI.^{8,9}

The worldwide prevalence of type 2 diabetes mellitus (DM) will increase from 4.0% in 1995 to more than 7% by the year 2050.^{10,11}

In addition, this disease is more common within specific groups of patients, not the least those presenting with coronary artery disease (CAD). Previous reports from the Euro¹² and China Heart Surveys,¹³ based on patients with acute and stable CAD, revealed that approximately one-third of them had known DM. Surprisingly, the association between RHR, a familiar and accessible clinical variable, and cardiovascular mortality has never been specifically assessed in patients with DM.

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The purpose of the present report from the Euro Heart Survey on Diabetes and the Heart is to test the association between RHR and cardiovascular events (CVE) in stable CAD patients with and without DM.

Methods

Between February 2003 and January 2004, the Euro Heart Survey on Diabetes and the Heart recruited 4961 patients with CAD at 110 centres in 25 European countries. Full details of the survey are reported previously.^{14,15} In brief, consecutive patients were screened for a diagnosis of CAD when admitted to hospital wards or visiting outpatient clinics at participating centres. All patients were assessed, investigated, and treated at the discretion of their responsible physicians, according to local institutional practice. Clinical characteristics, interventions, and results of laboratory tests at the time for recruitment were collected by means of a web-based case record form as were follow-up data. Of the 4961 originally recruited patients, 94% (4676) were followed, for at least 1 year (median: 374 days, Q1–Q3: 366–397), with respect to treatment, survival, and CVE (all-cause mortality, myocardial infarction, and stroke). To limit the autonomic influences on the cardiovascular system due to acute stress caused by the actual disease condition,¹⁶ the present report only included patients with stable CAD (Figure 1). As in previous reports from the Euro Heart Survey,¹⁷ to avoid considering patients that withdraw treatment within the year of follow-up, the medication use included in the present analysis was that prescribed at discharge and recorded at follow-up.

Definitions

Character of admission: on the basis of the clinical presentation at enrolment, the patients were categorized as having acute or stable CAD. Acute CAD was defined as not-prescheduled hospital admissions due to acute coronary syndromes, aggravated symptoms of heart failure, or arrhythmias. Stable CAD was defined as elective consultations in an outpatient clinic and scheduled hospital admissions for diagnostic procedures, treatment adjustments, or elective interventions related to CAD.

Glucometabolic state: the presence of known DM was recognized if this diagnosis was established prior to enrolment according to the WHO classification,¹⁸ reported in the medical records, declared

directly by the patient, or revealed by the use of glucose-lowering drugs.

RHR: RHR was recorded at enrolment following 5 min of sitting rest to be reported as the average of two measurements.

Statistical analysis

Continuous variables are expressed as medians with lower and upper quartiles (Q1–Q3), and categorical variables as counts and percentages. Continuous variables were compared between strata by means of analysis of variance, and categorical variables in contingency tables by means of Pearson's χ^2 test. The Kaplan–Meier curves were computed for all-cause mortality and the composite endpoint of CVE (including all-cause mortality, myocardial infarction, and stroke). The log-rank test was used to test for differences in the unadjusted survival curves. The Cox proportional-hazard regression was used to test correlation of 1-year events with RHR, DM state, and the interaction term of these two parameters. If the interaction term between RHR and DM was significant, the subsequent multiple Cox proportional-hazard regression models were to be performed on patients with and without DM separately. Forward- and backward-stepwise selection were performed to adjust the models for confounders detected from the baseline characteristics and medications at follow-up (Table 1). Assumption of proportional hazards was assessed and satisfied by visual inspection of the log-minus-log survival curves for the RHR quartiles distribution. A two-sided *P*-value of <0.05 was considered statistically significant; all analyses were performed with SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Ethical consideration

The protocol was approved by the Ethics Committee at Karolinska Institutet, Stockholm, Sweden, and National Survey coordinators took the responsibility for assuring compliance with the ethical requirements in each country. The patients were enrolled following an oral and/or written informed consent with respect to the local rules and were informed about the follow-up after 1 year.

Results

Of the 2608 patients with stable CAD, enrolled during an outpatient clinic or a scheduled hospital admission, 780 (30%) had known DM (Figure 1). Resting heart rate at enrolment was available in a total of 2507 (96%) patients: 1756 (96%) without and 751 (96%) with DM. Overall, median RHR was 70 (62–78; minimum 40, maximum 140) b.p.m.; 70 (60–76; minimum 40, maximum 140) and 75 (62–78; minimum 40, maximum 126) b.p.m., respectively, in patients without and with DM. Comparison of baseline characteristics and medications at follow-up within RHR quartiles in patients with and without DM is detailed in Table 1. One-year events are reported in Table 2 by RHR quartiles and by diabetic state. The Kaplan–Meier curves for all-cause mortality and survival free from myocardial infarction and stroke emphasize 1-year prognosis by RHR quartiles in the overall population and in patients with and without DM, respectively (Figure 2). The RHR quartile stratification was associated with 1-year outcome in the overall population (log-rank test: $P = 0.002$ and $P = 0.021$ for survival and CVE, respectively), whereas it did not correlate to all-cause mortality or CVE in patients without DM. In contrast, the RHR quartile stratification was associated with 1-year all-cause mortality (log-rank test $P = 0.032$) in patients with DM.

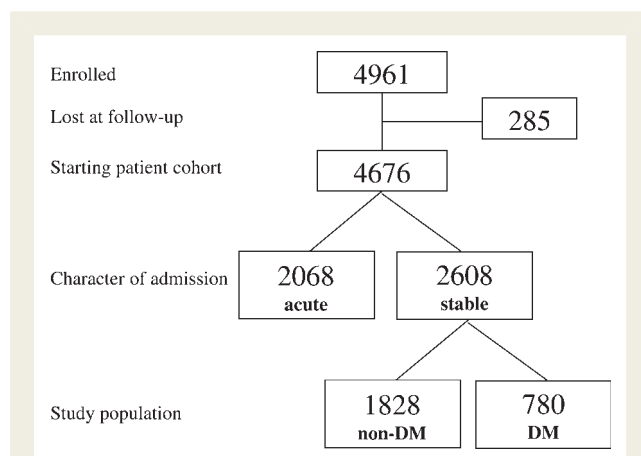


Figure 1 Description of the study population. DM, diabetes mellitus.

Table 1 Baseline characteristics and medications at follow-up (data presented as percentages if not otherwise stated) of patients with stable coronary artery disease by resting heart rate quartiles (Q1 ≤ 62, 62 < Q2 ≤ 70, 70 < Q3 ≤ 78, and Q4 > 78 b.p.m.) and diabetic state (P-value by analysis of variance and Pearson's χ^2 test for comparison of continuous and categorical variables between resting heart rate quartiles within diabetic state)

Variable	Total	Non-DM (n = 1756)					P-value	DM (n = 751)					P-value
		All	Q1	Q2	Q3	Q4		All	Q1	Q2	Q3	Q4	
Males	72	74	77	74	69	72	0.012	69	76	74	66	66	0.083
Median age (years)	66	66	64	65	67	67	0.001	68	68	66	70	68	0.127
Current smokers	16	17	14	17	17	20	0.065	12	15	9	12	12	0.314
Hypertension	67	62	60	60	69	63	0.063	77	72	82	74	82	0.086
Hyperlipidaemia	73	73	77	72	74	69	0.228	72	80	72	69	70	0.063
CVD	14	12	9	6	17	18	0.001	17	9	13	20	25	0.001
PAD	18	14	8	10	22	17	0.001	27	17	19	39	31	0.001
Previous													
CAD	25	25	21	21	29	31	0.001	26	23	19	38	26	0.001
CHF	25	21	11	16	30	33	0.001	33	21	20	45	41	0.001
PCI	56	55	51	56	57	56	0.229	57	58	49	65	56	0.019
CABG	32	35	42	39	27	30	0.001	26	27	28	23	25	0.675
Medications at follow-up													
BB	76	76	78	75	80	71	0.023	74	74	77	74	73	0.782
ACE-I/ARBs	68	64	60	63	69	67	0.022	79	75	68	84	84	0.062
Oral anti-PLTs	78	79	95	88	79	69	0.001	77	96	81	79	77	0.001
Statins	68	76	80	79	75	69	0.002	73	73	73	71	74	0.947

DM, diabetes mellitus; CVD, cerebrovascular disease; PAD, peripheral artery disease; CAD, coronary artery disease; CHF, congestive heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BB, β -blockers; ACE-I/ARBs, renin-angiotensin system blockers; PLTs, platelets.

Table 2 One-year events (shown as counts and %) stratified by resting heart rate quartiles (Q1–Q4) in the overall population and in patients without and with diabetes mellitus

	All-cause mortality			CVE		
	All	NDM	DM	All	NDM	DM
Q1 661 (510/151) ^a	14 (2)	11 (2)	3 (2)	42 (6)	29 (6)	13 (9)
Q2 600 (443/157) ^a	16 (3)	11 (2)	5 (3)	35 (6)	23 (5)	12 (8)
Q3 645 (438/207) ^a	21 (3)	11 (2)	10 (5)	60 (9)	33 (7)	27 (13)
Q4 601 (365/236) ^a	21 (3)	12 (3)	19 (8)	53 (9)	19 (5)	34 (14)
Total	82 (3)	45 (3)	37 (5)	190 (8)	104 (6)	86 (11)

NDM, patients without diabetes mellitus; DM, patients with diabetes mellitus; CVE, cardiovascular events.

^aPatients without and with diabetes mellitus, respectively.

Detailed results of the Cox regression models performed are reported in Table 3. In the unadjusted Cox regression model run on the total population, a 10-b.p.m. increase in RHR correlated with worse 1-year survival [hazard ratio (HR): 1.25, 95% confidence interval (95% CI): 1.11–1.40, $P < 0.001$] and combined CVE (HR: 1.10, 95% CI: 1.01–1.21, $P = 0.036$). The interaction term within RHR and diabetic state was associated with both 1-year survival (HR: 1.10, 95% CI: 1.04–1.16, $P < 0.001$) and

combined CVE (HR: 1.09, 95% CI: 1.06–1.13, $P < 0.001$). Adjusting for available confounders, RHR association with 1-year events did not retain statistical significance in patients without DM concerning both survival (HR: 0.97, 95% CI: 0.74–1.27, $P = 0.804$) and CVE (HR: 0.85, 95% CI: 0.71–1.01, $P = 0.068$). In contrast, a 10-b.p.m. increase in RHR was independently associated with 1-year survival (HR: 1.34, 95% CI: 1.06–1.69, $P = 0.015$) in patients with DM but not with 1-year combined CVE (HR: 0.99, 95% CI: 0.84–1.18, $P = 0.359$).

Discussion

The present report tests the association between RHR and CVE in stable CAD patients with and without DM. The main finding is that although high RHR was associated with worse 1-year survival in the total CAD population, the association, following adjustments for available confounders, only remained in patients with DM.

A significant correlation between RHR, a familiar and accessible clinical variable, and all-cause and cardiovascular mortality has been reported in the general population and in patients with various cardiovascular diseases.^{1–5} Diabetes mellitus being an increasingly prevalent disorder especially in patients with cardiovascular disease, and the fact that none of the previous observations were performed separating DM from non-DM patients may have been misleading. To the best of our knowledge, this is the first study testing the association between RHR and cardiovascular outcome comparing CAD patients with and without DM.

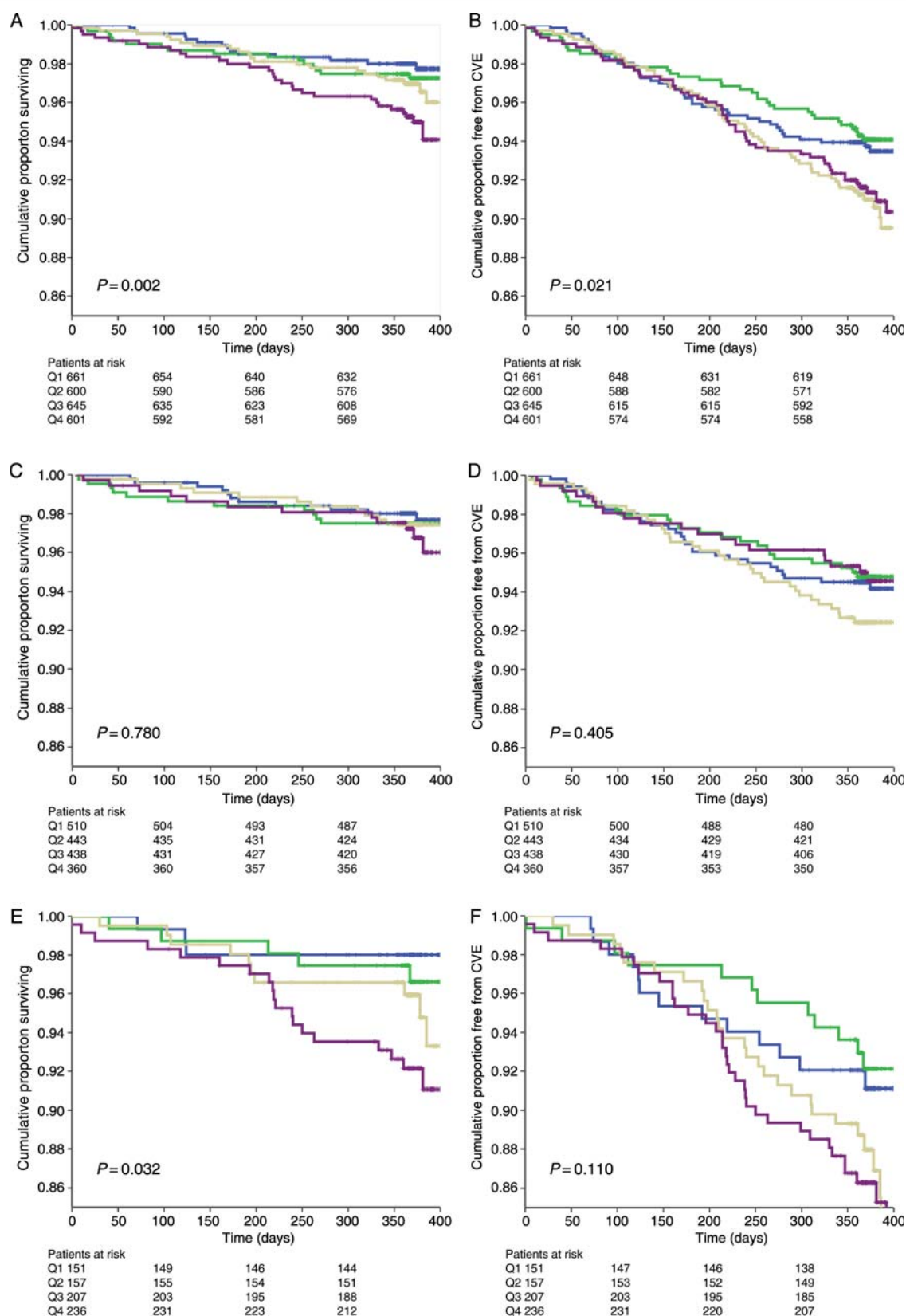


Figure 2 The Kaplan–Meier curves for survival (A, C, and E) and survival free from myocardial infarction and stroke (B, D, and F) by resting heart rate quartiles in the overall population (A and B) and in patients without (C and D) and with (E and F) diabetes mellitus (blue, Q1 \leq 62; green, 62 < Q2 \leq 70; yellow, 70 < Q3 \leq 78; purple, Q4 > 78 b.p.m.; P -value by log-rank test).

Table 3 Upper part: Cox proportional-hazard regression testing the relation between resting heart rate in 10 b.p.m., the presence of diabetes mellitus, and the interaction between these two parameters with 1-year all-cause mortality and cardiovascular events; lower part: crude and adjusted analysis of the relation between RHR in 10 b.p.m. and all-cause mortality and combined cardiovascular events in patients with stable coronary artery disease without and with diabetes mellitus

Population	Parameter	HR	All-cause mortality 95% CI	P-value	HR	CVE 95% CI	P-value
Total	RHR/10 b.p.m.	1.25	1.11–1.40	<0.001	1.10	1.01–1.21	0.036
	DM	1.85	1.22–2.82	0.004	1.91	1.44–2.53	<0.001
	Interaction term ^a	1.10	1.04–1.16	<0.001	1.09	1.06–1.13	<0.001
Non-DM	RHR/10 b.p.m.	1.15	0.97–1.37	0.110	1.04	0.91–1.19	0.555
Adjusted ^b	RHR/10 b.p.m.	0.97	0.74–1.27	0.804	0.85	0.71–1.01	0.068
DM	RHR/10 b.p.m.	1.41	1.14–1.74	<0.001	1.14	0.98–1.33	0.086
Adjusted ^c	RHR/10 b.p.m.	1.34	1.06–1.69	0.015	0.99	0.84–1.18	0.359

HR, hazard ratio; 95% CI, 95% confidence interval. Other abbreviations as in previous tables.
^aResting heart rate (10 b.p.m.) multiplied by diabetic status.
^bAdjusted for gender; age; cerebrovascular disease; peripheral artery disease; previous coronary artery disease, congestive heart failure, CABG; β -blockers, ACE-inhibitors/ARBs, oral antiplatelets, and statins at follow-up.
^cAdjusted for cerebrovascular disease; peripheral artery disease; previous coronary artery disease, congestive heart failure, PCI; oral antiplatelets at follow-up.

Oxygen consumption is heart-rate proportional,¹⁹ and in previous experimental studies, high heart rate has been related to arterial rigidity,²⁰ extent and progression of coronary artery atherosclerosis,^{21,22} and likelihood of disrupting atherosclerotic plaques.²³ In the case of concomitant DM, there are several additional reasons that may increase the negative prognostic influence of a high RHR. Hyperglycaemia enhances the tendency for plaque destabilization by decreasing endothelium-derived nitric oxide availability²⁴ and synthesis of collagen and by increasing reactive oxygen species²⁵ and matrix metalloproteinases production.²⁶ In addition, the dominant metabolic pathway for myocardial energy production in DM patients relies on non-esterified fatty acids, which compared with glucose oxidation, requires higher basal oxygen levels.²⁷ So far, only few studies addressed the prognostic role of RHR in diabetic-specific populations, and no studies focused on DM patients with cardiovascular disease. A previous experience on 523 DM patients (221 with type 1 and 302 type 2 DM) related RHR to 20-year increased mortality only within subjects with type 2 DM.²⁸ Further support derives from 475 type 2 diabetic patients included in the Bremen Diabetes Study.²⁹ In this observational study, an elevated heart rate (>75 b.p.m.) related to a 5-year increase in cardiovascular death (HR: 3.3, 95% CI: 1.33–8.19). The aforementioned reasons all support the finding of the present report that high RHR, in DM patients, may relate to a more dismal survival.

Cardiac autonomic neuropathy is a common chronic complication in patients with DM. Despite this, high RHR by itself is not considered to provide a reliable diagnostic criterion of cardiac autonomic neuropathy. However, in the absence of other signs, it may surely reflect a relative increase in the sympathetic tone associated with vagal impairment.³⁰ This condition, based on a meta-analysis of 15 studies including 2900 subjects with DM, has been related to a three times greater relative risk of mortality.³¹ The difference between DM and non-DM patients with CAD in the association of RHR with CVE may, therefore, be

that increasing RHR reflects a parasympathetic disturbance and adrenergic dominance more easily determinable, and transferable in 1-year outcome, within patients with DM. In this perspective, it is of interest that available information reports on the association between intensive DM management and lower RHR in type 1 diabetes.³²

The finding that high RHR was not independently associated with 1-year survival in patients without DM most probably relies on the two following points. First, high RHR presents a plausible minor harmful effect in a non-DM than in a DM setting. Second, a follow-up duration of 1 year may be a too short-term period to detect significant differences in events of a relatively 'low'-risk population as that of without DM.

Study limitations

The present report is based on a secondary utilization of an existing material that offered an opportunity, not often available in similar settings, to make the analyses on which the article is focused. The population included and the 1-year follow-up may be experienced as limited for an epidemiologic study. Still, the findings generate a hypothesis which may be further elucidated in greater populations. Relevant differences in baseline characteristics are present between patients with and without diabetes. Despite adjusting the multiple Cox proportional-hazard regression models for available confounders differences in baseline characteristics cannot be excluded as, at least, partial reasons for the findings.

In conclusion, the present report based on a large European survey on patients with CAD is the first to reveal that the association between RHR and CVE seems to be limited to those with DM. In light of the present data, previous observations on the importance of RHR for cardiovascular prognosis may have been misleading since they were not controlled for the DM state. The present finding warrants consideration when planning future investigations.

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Conflict of interest: none declared.

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